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An Examination of the Phase Transition Thermodynamics of (*S*)- and (*RS*)-Naproxen as a Basis for the Design of Enantioselective Crystallization Processes

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ABSTRACT

A detailed experimental analysis of the phase transition thermodynamics of (*S*)-naproxen and (*RS*)-naproxen is reported. Vapor pressures were determined experimentally via the transpiration method. Sublimation enthalpies were obtained from the vapor pressures and from independent TGA measurements. Thermodynamics of fusion which have been well-studied in the literature were systematically remeasured by DSC. Both sublimation and fusion enthalpies were adjusted to one reference temperature, $T = 298$ K, using measured heat capacities of the solid and the melt phase by DSC. Average values from the measurements and from literature data were suggested for the sublimation and fusion enthalpies. In order to prove consistency of the proposed values the vaporization enthalpies obtained by combination of both were compared to vaporization enthalpies obtained by the group-additivity method and the correlation-gas chromatography method. The importance of reliable and precise phase transition data for thermochemical calculations such as the prediction of solid/liquid phase behaviour of chiral compounds is highlighted.

Introduction

The production of pure enantiomers is important for the food and drug industry and increasingly for the agrochemical sector. It has been reported that about 56% of the marked drugs are chiral.[1] Crystallization processes have been reported to be especially efficient for large-scale enantioseparation.[2] Solubilities play an important role for process design as they define feasibility and productivity of a crystallization process. Naproxen as well as about 90%-95% of the chiral systems[3] can form a stoichiometric 1:1 molecular racemic compound, (*RS*)-naproxen (see Fig. 1, left).

The eutectic composition, x_{eu}, defines the boundary between the areas where pure enantiomer or the racemic compound can be crystallized from solution (indicated as gray area in Fig. 1, left). Hence, for process design of such systems, the solubility of the enantiomers, $x_{(S)}$ and $x_{(R)}$, and of the molecular compound, $x_{(RS)}$, as well as the eutectic composition in solution are characteristic information. In earlier investigations, we studied solubility behavior and crystallization-based enantioseparation on several substances, for example, propranolol hydrochloride,[4] 3-chloromandelic acid,[5] and guaifenesin[6] on an experimental basis. However, especially in early stages of process design, the available amount of substance is often scarce for detailed experimental studies. Solubility prediction can support and complement experimental examinations.

To access solubility by computational methods, the free energy change of the solution process, $\Delta_{cr}^{sol}G_{sol}^{\circ}$, has to be split up into accessible quantities by a thermodynamic cycle. The solution process can be thermodynamically described by either transferring the molecule from the solid crystal via (1) the subcooled melt or (2) the gas phase into the solution (illustrated in Fig. 1, right).[7] The 2 thermodynamic cycles have been compared in a previous study[8] for chiral lactide where experimental melting properties and sublimation enthalpies are used to calculate solubilities and to estimate the eutectic composition in a solvent mixture. For a merely predictive method, besides solvent interaction-based

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